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Epidemiology, clinical characteristics, and outcome of candidemia: experience in a tertiary referral center in the UK☆

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SUMMARY

Objectives: To review the epidemiology of candidemia in a UK tertiary referral center.
Methods: Clinical and laboratory data from patients with candidemia were collected prospectively from October 1, 2005 to June 30, 2008 (a 33-month period).
Results: A total of 107 episodes were identified. The incidence was 10.9 episodes/100 000 bed-days. The most common predisposing factors were the use of broad-spectrum antibiotics (92%), the presence of an intravascular device (IVD) (82%), admission to an intensive care unit (ICU) (51%), and recent surgery (50%). Non-*Candida albicans* species accounted for 58% of the episodes, which is higher than the percentage reported from other UK centers. *C. albicans* was the most common species, accounting for 43% of episodes, followed by *C. glabrata* (31%) and *C. parapsilosis* (20%). Overall *C. tropicalis*, *C. krusei*, *C. norvegensis*, and *C. lusitaniae* caused 7% of episodes. The crude 30-day mortality rate was 37%. Advanced age ($p = 0.003$) and the presence of septic shock ($p = 0.038$) were associated with mortality.
Conclusions: Candidemia continues to be associated with a high mortality. Preventative measures should be targeted against high-risk hospitalized patients, especially those in ICUs, the elderly, and those undergoing major surgery. Local surveillance of candidemia is important to optimize management.

1. Introduction

The incidence of disseminated candidiasis including blood stream infection has increased significantly over the past decades.[1–4] *Candida* species are the most common cause of invasive fungal infections in hospitalized patients and are the fourth most common cause of nosocomial bloodstream infections in the USA.[5,6] Candidemia is associated with a prolonged hospital stay, resulting in increased costs, and a high mortality of 25–60%.[3,7–14] *Candida spp* have been reported as the only organisms that independently influence the outcome of nosocomial blood stream infections (estimated odds ratio for mortality = 1.84).[15]

The epidemiology of candidemia is changing worldwide with an increase in the proportion of non-*Candida albicans* species.[3,16] Amongst most species causing bloodstream infections, fluconazole resistance is relatively uncommon, with the exception of *Candida glabrata*.[17] The clinical manifestations of invasive candidiasis are non-specific, and the microbiological diagnosis remains a challenge with a high rate of false-negative blood culture results.[18] The value of other diagnostic tests remains controversial.

We investigated the epidemiology, predisposing factors, and outcome of candidemia in our institution, with an aim to improve the management of candidemia.

2. Patients and methods

University Hospitals Birmingham Foundation Trust is a 1200-bed teaching hospital providing a wide range of services, including acute medical and surgical care and regional and tertiary care for burns, trauma, and orthopedic surgery, cancer, neurology/neurosurgery, cardiac surgery, and transplantation. There are no obstetric/gynecology or pediatrics units in the Trust. The Trust provides 54 000 admissions annually. There are four intensive care units (ICU) with a total of 75 beds.

A prospective observational study of all cases of candidemia was carried out from October 1, 2005 to June 30, 2008 (a 33-month period). All episodes of candidemia were identified through the laboratory computer system (TelePath). Data on the demographics of patients, underlying medical conditions, information on immunosuppression, results of relevant investigations, including inflammatory markers, and information on the details of antimicrobial therapy were collected through the hospitalelectronic Prescribing Information and Communication System (PICS) and clinical

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microbiology notes, as well as the patient's notes. Patients were followed-up until discharge/death. Clinical details, presence of an intravascular device (IVD), and a history of major surgery in the 30 days prior to the occurrence of candidemia were collected through the clinical microbiology records. Records of readmission and outpatient visits, laboratory results following such events, and outcome were searched through the PICS and the laboratory computer system for a minimum period of 6 months following discharge. No follow-up was undertaken in the absence of readmission/outpatient visits following discharge. Data were collected on a review form for each episode, which was subsequently entered electronically onto a database (Excel, Microsoft).

Blood cultures were processed according to routine practice using the automated blood culture system BACTEC 9240 (Becton Dickinson, Sparks, MD, USA) and BacT/ALERT 3D^{TM} (bioMérieux, Marcy-l'Etoile, France; after 1 March 2008), with an average incubation period of 5 days. No specific blood culture bottles were used for the isolation of fungi. As part of the routine blood culture processing service, BD BACTEC Plus Aerobic/F* and BD BACTEC plus Anaerobic/F* bottles were used for the BACTEC system, whereas BacT/ALERT SA and BacT/ALERT SN bottles were used for the BacT/ALERT system. Blood cultures were incubated for a period of 14 days when specific information including the possibility of fungal infection or the presence of antifungal therapy was provided with the microbiology request form. No terminal subculture was undertaken, according to routine practice. A positive blood culture with yeasts on Gram staining was subcultured onto Can 2 plates (bioMérieux, Marcy-l'Etoile, France). Isolates were identified as *C. albicans* with specific colored colonies. Non-*C. albicans* isolates were speciated by a commercial identification system, Candida Auxacolor 2 (Bio-Rad, Marnes-la-Coquette, France) or API 20C Aux (bioMérieux, Marcy-l'Etoile, France). Those isolates that could not be identified by the above systems were sent to the Mycology Reference Laboratory (Bristol, UK).

Antifungal susceptibility tests were performed by the Mycology Reference Laboratory. Interpretive criteria used for fluconazole, itraconazole, voriconazole, and caspofungin were in accordance with the Clinical and Laboratory Standards Institute guidelines (CLSI, Wayne, PA, USA). For amphotericin, the interpretation was based on expert opinion.

2.1. Statistical analysis

Categorical variables were compared between groups with Fisher's exact test and continuous variables with the Kruskal–Wallis test. Stepwise binary logistic regression analysis, with mortality as the dependent variable, was used for multivariable analysis, and the results are presented as estimated odds ratio (OR) with associated 95% confidence intervals (CI) and *p*-values. All statistical analyses were performed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

2.2. Definitions

At least one blood culture with growth of *Candida spp* was included as an episode of candidemia. An additional episode of candidemia 2 weeks after the previous episode with resolution of clinical features of sepsis in the intervening period was considered as a separate episode.

An IVD was defined as the focus of candidemia if a *Candida* species was grown from an IVD tip (when received by the laboratory) during an episode of candidemia.

Neutropenia was defined as an absolute neutrophil count $\leq 0.5 \times 10^9$/l. Septic shock was defined in the presence of a systolic blood pressure of <90 mmHg, a diastolic blood pressure of <60 mmHg, or fluid/inotrope requirement to maintain a blood pressure above these levels.

Antifungal therapy was defined as inappropriate if the isolated *Candida spp* was resistant or likely to be resistant (i.e., fluconazole for *Candida krusei*) to the chosen antifungal agent, or if an active antifungal agent was used with inadequate dosages (<400 mg of fluconazole/day). Therapy with an inadequate dose of an antifungal agent with an intermediate/dose-dependent susceptibility to the isolated *Candida spp* was also defined as inappropriate.

Candidemia as the attributed cause of death: this was defined in the presence of continuing sepsis leading up to the death and the lack of isolation of another pathogen.

3. Results

One hundred and seven episodes of candidemia were identified in 102 patients. The rate of candidemia was 10.9 episodes/100 000 bed-days. Candidemia was detected at a median of 14 days following hospital admission. Patient baseline characteristics and clinical details stratified by *Candida spp* are reported in Table 1. The median patient age was 55 years (for all episodes). Most episodes of candidemia were hospital-acquired ($n = 94$, 88%). Fifty-five (51%) episodes were associated with the ICUs. Immunocompromised conditions and neutropenia were uncommonly associated with candidemia (Table 1). Most episodes were associated with surgical specialties ($n = 67$, 63%). In this group, gastrointestinal (GI) surgery was the predominant specialty (18 of 67, 27%), followed by cardiac surgery (15 of 67, 22%). Most patients had previously been exposed to broad-spectrum antibiotics ($n = 98$, 92% episodes).

Patients presented with septic shock in 14 (13%) episodes. Nine of the 14 episodes (64%) occurred in patients who were admitted to ICUs. No appropriate empirical antifungal therapy was initiated for any of the above episodes.

The time interval to detection of candidemia following collection of a blood culture sample varied widely from 0 to 8 days, with a median of 2 days (interquartile range 2–3 days).

The distribution of *Candida spp* is shown in Figure 1. One of the 107 candidemia episodes was caused by a mixture of two types of *Candida spp*. *C. albicans* was the most common species isolated ($n = 46$, 43%), followed by *C. glabrata* ($n = 33$, 31%) and *Candida parapsilosis* ($n = 21$, 20%). Non-*Candida albicans* species accounted for 58% of the episodes. Overall, *C. tropicalis*, *C. krusei*, *C. norvegensis* and *C. lusitaniae* caused 7% of the episodes. There was no difference between the major *Candida spp* in relation to age of patients ($p = 0.26$), sex ($p = 0.13$), presence of an IVD ($p = 0.07$), history of recent surgery ($p = 0.09$), or severity of sepsis ($p = 0.45$). The following significant differences were found across the *Candida spp*: *C. albicans* was the most common species associated with ICU infections ($p = 0.035$); *C. glabrata* was most commonly associated with GI tract disease ($p = 0.015$) and least often with an IVD focus ($p = 0.003$) and with burns ($p = 0.029$). In 56 (52%) episodes, colonization with a *Candida spp* was evident around the time of candidemia.

Overall resistance to antifungal agents was low. Resistance to amphotericin was not detected in any of the Candida strains. All *C. albicans* isolates were susceptible to amphotericin, voriconazole, fluconazole, itraconazole, and caspofungin. Overall 89/106 (84%) Candida strains were susceptible to fluconazole and 15/106 (14%) strains exhibited dose-dependent susceptibility (or intermediate susceptibility) to fluconazole. Resistance to fluconazole was detected in two strains (one *C. glabrata* and one *C. krusei*). Dose-dependent (or intermediate) susceptibility to fluconazole was detected in 13/33 (39%) *C. glabrata* strains.

Appropriate antifungal therapy was initiated irrespective of timing in 87 (81%) episodes, and in 72 (67%) episodes the therapy was continued for a minimum period of 7 days; there were

Table 1
Demographics clinical characteristics, antifungal therapy, and outcome of candidemia by the three most common *Candida* species

Characteristic	All episodes (n = 107)	*C. albicans*[a] (n = 45)	*C. glabrata* (n = 33)	*C. parapsilosis* (n = 21)	p-Value[b]
Median age (range), years	55 (17–95)	56 (19–95)	58 (23–89)	46 (17–82)	0.26
Male	52 (49)	20 (44)	21 (64)	8 (38)	0.13
Female	55 (51)	25 (56)	12 (36)	13 (62)	0.13
Hospital-acquired	94 (88)	42 (93)	29 (88)	15 (71)	0.052
ICU-acquired	55 (51)	29 (64)	12 (36)	9 (43)	0.035
Any underlying condition[c]	90 (84)	35 (78)	28 (85)	20 (95)	0.22
Diabetes	18 (17)	7 (16)	5 (15)	4 (19)	0.88
Malignancy	31 (29)	12 (27)	11 (33)	5 (24)	0.74
GI tract disease	36 (34)	10 (22)	18 (55)	7 (33)	0.015
Immunocompromised	16 (15)	5 (11)	8 (24)	2 (10)	0.24
Neutropenia	4 (4)	1 (2)	2 (6)	0	0.59
Burns	10 (9)	7 (16)	0	3 (14)	0.029
Chronic renal failure	11 (10)	3 (7)	5 (15)	3 (14)	0.38
Recent surgery	53 (50)	26 (58)	16 (48)	6 (29)	0.09
IVD in situ	88 (82)	38 (84)	22 (67)	19 (90)	0.07
IVD – focus of infection	40 (37)	22 (49)	5 (15)	11 (52)	0.003
Severe sepsis and septic shock	14 (13)	4 (9)	6 (18)	2 (10)	0.45
Appropriate antifungal therapy initiated	87 (81)	43 (96)	21 (64)	16 (76)	<0.001
Appropriate therapy completed (minimum 7 days)	72 (67)	36 (80)	16 (48)	15 (71)	0.013
Appropriate empirical therapy started within 24 h of collection of blood culture	16 (15)[d]	9 (20)	3 (9)	4 (19)	0.43
Crude mortality					
Death within 7 days of candidemia	21 (20)	7 (16)	11 (33)	2 (10)	0.07
Death within 30 days of candidemia	40 (37)	13 (29)	19 (58)	6 (29)	0.025
Attributable mortality					
Death within 7 days of candidemia	16 (15)	5 (11)	8 (24)	2 (10)	0.24
Death within 30 days of candidemia	23 (21)	6 (13)	11 (33)	4 (19)	0.12

ICU, intensive care unit; GI, gastrointestinal; IVD, intravascular device. All numbers in brackets represent percentages unless stated otherwise.
[a] One episode with mixed growth of *C. albicans* and *C. krusei* is excluded.
[b] Wherever there is a significant difference between the three species, *C. albicans* and *C. glabrata* are significantly different. In addition, for IVD as the focus of infection, *C. glabrata* and *C. parapsilosis* are significantly different, and for antifungal therapy, *C. albicans* and *C. parapsilosis* are significantly different.
[c] Includes the presence of chronic heart or lung disease or any of the medical conditions specified below.
[d] One patient was already on appropriate antifungal therapy as a result of previously detected candidemia from the transferring hospital.

significant differences between the species (see Table 1). In only 16 (15%) episodes was appropriate antifungal therapy initiated within 24 h of collection of the first set of blood cultures with a *Candida* species. The following antifungal agents were used either as the sole agent throughout the course of treatment, or in a sequential pattern resulting in the use of multiple agents for a single episode: fluconazole was used most often (n = 65, 61%), followed by amphotericin B-based preparations (n = 30, 28%), caspofungin (n = 31, 29%), and voriconazole (n = 8, 7%). Amphotericin lipid formulations were mostly used amongst the amphotericin B group (n = 28, 93%).

In 88 (82%) episodes, an IVD was in situ at the time of candidemia; implanted IVDs were in situ in 23 (26%) of these episodes. In the presence of an IVD, advice was given for its removal and this was implemented whenever possible. The IVDs were removed in 78/87 (90%) cases, but only 73 of the 87 (84%) tips were received by the laboratory. *Candida spp* were isolated from the IVD tips in 40 (37%) episodes, therefore confirmed as the foci of candidemia. In 10 episodes, no record of a removal of the IVD was available. In five of these patients the reasons for failure to remove IVDs were as follows: one patient was already diagnosed to have endocarditis as the focus of candidemia, a second patient was clinically suspected to have deep-seated candidiasis of the oral cavity, a third patient died before reporting of candidemia, the fourth patient was pre-morbid, and the fifth patient was hemodialysis-dependent with a poor prognosis and difficult vascular access. Three of the implanted IVDs were not removed.

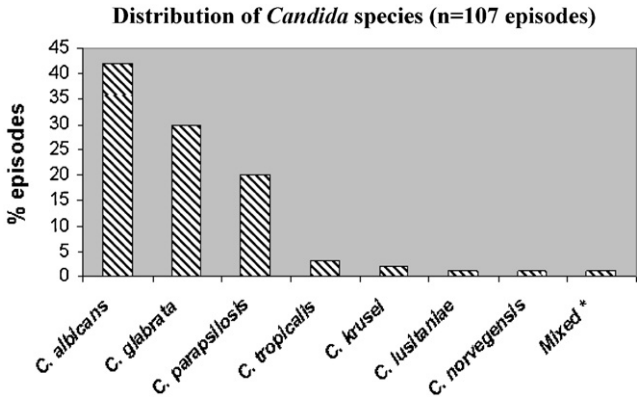

Figure 1. Distribution of *Candida* species (*C. krusei* and *C. albicans*).

The 30-day crude mortality was 37% and the attributable mortality was 21% (Table 1). The mortality rate in the group receiving appropriate empirical antifungal therapy within 24 h of collection of a blood culture positive for a *Candida spp* and in those receiving therapy after a positive blood culture report was not significantly different.

Nine of the 14 (64%) episodes associated with septic shock resulted in death at 30 days of candidemia (p = 0.037). Logistic regression analysis identified the association of advanced age (OR 1.04, 95% CI 1.01–1.06; p = 0.003) and septic shock (OR 3.77, 95% CI 1.08–13.20; p = 0.038) with crude mortality at 7 days and 30 days. The above analysis also revealed the association of advanced age (OR 1.06, 95% CI 1.02–1.09; p = 0.003) and septic shock (OR 5.49, 95% CI 1.45–20.84; p = 0.012) with attributable mortality at 30 days. An association of a specific *Candida spp* with mortality was not identified in the multivariable analysis.

Six patients (6%) had recurrent episodes of candidemia, of whom five had the recurrences during the study period and one after completion of the study period. One further patient had persistent infection and died with an unresolving mediastinitis following 12 weeks of candidemia.

4. Discussion

Because of the lack of sensitivity of blood cultures, estimates of invasive candidiasis based on positive blood cultures are artificially low. The epidemiology of candidemia with regards to the incidence as well as C*andida* species distribution, varies markedly from country to country as well as from region to region.[19] Recent reports on rates of candidemia have ranged from 0.2 to 0.5/1000 admissions and 0.31 to 1.4 episodes per 10 000 patient-days.[9,10,12,13,20,21] Our rate, which equates to 1.09 episodes/10 000 bed-days, is higher than rates reported previously from the UK and Europe.[10,20,21] We noted a high incidence in the ICUs (51%) and surgical specialties, especially from GI and cardiac surgery. Although *C. albicans* was the predominant species, the proportion of non-*C. albicans* species, particularly *C. glabrata*, was higher than reported from other centers, including centers in the UK.[1,3,10,13,21]

The 30-day crude mortality of 37% is higher than a recent report from the USA, but similar to previous reports from Europe.[9,10] Five patients (5%) died within 24 h of blood culture collection and before detection of candidemia. Death was attributed to candidemia in the above patients. Attributable mortality due to candidemia has been shown to be significant, ranging from 14% to 49%.[9,22] Both the crude and attributable rates of 37% and 21% in our study are likely to be underestimations, as death following transfer or discharge from the hospital was not searched for and death occurring after 30 days of candidemia was not included in this group. Similarly our recurrence rate of 6% is probably an underestimation, as patients were not actively followed up following discharge or transfer to another hospital. Moreover relapse/recurrence without a positive culture for Candida was not included in this group.

Our estimation of Candida colonization during an episode of candidemia in 52% of the episodes may have been an underestimation, as routine surveillance cultures for detection of microorganisms are not carried out in high-risk patients in our institution. Similar to other studies, we noted a common association of an IVD focus with candidemia.

An association of *C. glabrata* with advanced age and high mortality has previously been reported.[10,23,24] We observed an association of underlying GI disease and lack of an IVD focus with candidemia due to *C. glabrata*. The association of *C. glabrata* with increased mortality was not evident in the multivariable analysis in our study.

C. albicans has been reported by others to be associated with a high mortality.[3,23] In contrast to these reports, multivariable analysis in our study showed a lack of association of a specific *Candida spp* with mortality.

The absence of antifungal therapy has been associated with higher mortality in various studies.[3,12,24] A delay in initiation of fluconazole therapy in hospitalized patients with candidemia has also been shown to result in a significantly high mortality.[25,26] Our observation of the lack of association of mortality with delay in initiation of antifungal therapy may have been due to the small number of patients receiving appropriate empirical antifungal therapy ($n = 14$, 13%). We noted an association of septic shock with mortality in the multivariable analysis. None of the patients with septic shock had received appropriate empirical antifungal therapy. This observation combined with the delay in the laboratory detection of candidemia highlights the need for heightened awareness of invasive candidiasis/candidemia and the timely initiation of antifungal therapy in high-risk groups.

In conclusion, we observed candidemia as mostly hospital-acquired and an important cause of morbidity and mortality. The epidemiology of candidemia is changing, with our observation of non-*C. albicans* species as frequent causes of candidemia. IVDs, admission to the ICU, and recent major surgical procedures are commonly associated with candidemia. Advanced age and presence of septic shock are significantly associated with mortality, highlighting the need for awareness of candidemia and prompt initiation of antifungal therapy in these groups. Local surveillance of the epidemiology of candidemia is essential to identify subsets of high-risk patients and the pattern of causative *Candida spp* in order to formulate guidelines for optimal management.

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